REMARKS

Claims 1 and 3 are pending after entry of this paper. Claims 1 and 3 have been rejected. Claims 2 and 4 have been cancelled without prejudice. Applicants reserve the right to pursue cancelled claims in a continuing application.

Claim 1 has been amended to delete the phrase "a composition comprising, as an active ingredient" and add the phrase "to a patient suffering from pemphigus." Support may be found throughout the instant specification.

Claim 3 has been amended to delete the phrase "a composition comprising, as an active ingredient" and add the term "recurrence" and the phrase "to a patient who previously suffered from pemphigus." Support may be found throughout the instant specification, for instance, Example 2.

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §112

Claim 3 stands rejected under 35 U.S.C. §112, first paragraph for allegedly lacking of enablement. Specifically, the Examiner contends that the application as filed allegedly does not teach one skilled in the art how to make and use the information that some people are predisposed to pemphigus or to prevent the reoccurrence of the disease. (Office Action – page 3). Applicants respectfully disagree.

Applicants readily describe a composition "to prevent the development of pemphigus by preventively administering a CD40L antagonist to patients who are likely to suffer from recurrence of pemphigus." (See page 1 of the instant application). As an initial matter, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claim 3 to add the term "recurrence" and the phrase "to a patient who previously suffered from pemphigus." Applicants assert that as a matter of law,

> [a] single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. (See MPEP 2164.04; emphasis added)

The Examiner contends that "[t]he problem here is that applicant has not provided direction in the application as-filed to teach the skilled artisan how to make and use the information that certain people were predisposed to pemphigus or to utilize anti-CD40L antibodies to prevent the reoccurrence of the disease." (Office Action - Page 3). However, applicants respectfully assert that this observation is inconsistent with the instant disclosure.

Applicants describe in the **working** Example, how "[t]he preventive effect on pemphigus by the administration of MR1 antibody [anti-CD40L antibody]" was examined and evaluated. (See Example 2 of the instant specification). Specifically, applicants "[e]xamined whether the transferred splenocytes were capable of inducing immunological tolerance to Dsg3 when MR1 antibody was preventively administered so that CD40L was present at the time of inducing immune response to Dsg3." (See *Id*, page 12).

> [P]roduction of the anti-Dsg3 antibody was confirmed in the control group 14 days after the transfer, while any apparent antibody production or phenotype was not observed at all throughout the observation period of 66 days in the MR1-administered mice (Fig. 1). In addition, weight loss, hair loss in resting period and the immediate suprabasal acantholysis which is a pathohistological feature of PV [pemphigus] was observed in the

> control group, whereas neither weight loss nor symptoms of PV [pemphigus] was observed in the MR1 [anti-CD40L] administered group. The MR1 antibody apparently showed a preventive effect on PV [pemphigus]." (See *Id*, page 12; emphasis added).

One skilled in the art, contrary to the Examiner's contention, would not and could not doubt that the applicants provide ample support for a preventive effect of MR1 (anti-CD40L) antibodies on pemphigus in the art-recognized mouse models of pemphigus onset. Applicants respectfully direct the Examiner's attention to Example 2, which describes the mouse model.

However, the Examiner also questions the correlation of a mouse model to human diseases by alleging that "[w]ith respect to *in vivo* studies, animal models validate concepts based on studies of human disease, such studies are limited to the 'acute' as opposed to 'chronic' nature of the disease." (Office Action – page 4). However, applicants respectfully assert that such misguided observation by the Examiner could then be incorrectly made of every single animal model ever developed and constitute a mere speculation. The court upheld Applicants' position that

> [a]n … *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.
>
> In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (See MPEP 2164.02).

In fact, to demonstrate the preventive capabilities of the claimed invention, applicants describe the use of autoantigen-knockout mice, which are recognized in the art to

represent an active autoimmune disease model for pemphigus (Amagai, et al. *The Journal of Clinical Investigation* 105(5):625-631, 2000; previously submitted). The Examiner is invited to provide any evidentiary support to demonstrate that this autoantigen-knockout mouse model would not in fact be recognized by one of ordinary skill in the art as a model for onset and progression of pemphigus, anything less than that is merely speculative.

Furthermore, the Examiner states that the applicants have "…not sufficiently addressed the unpredictability and inconsistency of treating patients with pemphigus, as evidenced by The Merck Manual of Diagnosis and Therapy, Seventeenth Edition…" (Office Action – Page 3), and further states that according to the Merck Manual

> "[P]emphigus is a serious disease with an inconsistent and unpredictable response to therapy and that the aim of **treatment** is to stop the eruption of new lesions. See Treatment on page 829. Therefore, the treatment of pemphigus is drawn to the treatment of the disease and its associated lesions subsequent to an individual being diagnosed with pemphigus and not as a preventative agent of the disease itself, as recited in the current claims." (Office Action – page 4; emphasis added).

Applicants respectfully disagree. Applicants assert that the claim 3 as presently amended is directed to preventing pemphigus in patients who are likely to suffer from recurrence (*i.e.*, exacerbation) of pemphigus, which was successfully demonstrated in a working example 2 on a mouse-model of pemphigus. Hence, the description in the Merck Manual cited above (*i.e.*, "…the aim of treatment is to stop the eruption of new lesions") is immaterial in the context of the claim because the Merck Manual concentrates on presently available treatments with steroids, which are dangerous and require such stringent guidelines as presented by the Examiner. Whereas, applicants have discovered a novel method of treatment and prevention of pemphigus based on a highly specific immunosuppressant therapy unrelated to the use of steroids. Thus, one skilled in the art would not apply the same guidelines as recited in the Merck Manual

intended for the use with a non-specific immunosuppressant agents to a highly specific immunosuppressant therapy based on administering anti-CD40L antibodies of the present invention. Therefore, applicants assert that the reliance on the Merck Manual in the context of the current invention is misplaced.

For the reasons stated above, at the time of the invention, one skilled in the art, having read the instant specification, would understand that the claimed method of treating and preventing pemphigus would not necessitate undue experimentation to make and/or use the same, and would be fully enabled to practice the claimed invention. Reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph are respectfully requested.

Response to Rejections under 35 U.S.C. §102(b)

Claims 1 and 3 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 6,001,358 to Black, et al. ('358 patent). Specifically, according to the Examiner, the '358 patent allegedly discloses anti-CD40L antibody and therapeutic compositions thereof (Office Action – page 6). Accordingly, the Examiner alleges that the claimed invention is anticipated by such disclosure. Applicants respectfully disagree.

As previously noted in the response of June 29, 2007, the '358 patent characterizes humanized antibodies to human gp39 (also called CD40L; Column 3, line 46) that could potentially be used to treat 141 autoimmune and non-autoimmune ailments where one of them happens to be pemphigus (para. bridging columns 32 and 33). The '358 patent provides no

support for this assertion and lacks any examples (working or prophetic) of treatment of any disorder.

For the Examiner's convenience, applicants recite the following minimum requirement expected by the court from the allegedly anticipating prior art reference:

> In order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. *Amgen Inc. v. Hoechst Marion Roussel*, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003); *Helifix, Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed. Cir. 2000); *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).
>
> Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention. See *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1057 (Fed. Cir. 2003)

Therefore, the proper issue in the present case contrary to the Examiner's contention (Office Action – page 6) is not to prove efficacy of anti-CD40L against pemphigus, but whether or not the '358 patent is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention. *Impax Laboratories Inc. v. Aventis Pharmaceuticals, Inc.*, 81 USPQ2d 1001 (Fed. Cir. 2006). Specifically, whether the '358 patent enables a person of ordinary skill in the art to treat pemphigus with anti-CD40L antibody. The court held that when a reference discloses a class of ailments, *i.e.*, a genus, a person of ordinary skill in the art should be able to "at once envisage each member of th[e] . . . class" for the individual ailment, *i.e.*, species, to be enabled. *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). However, if the members cannot be envisioned, the reference does not disclose the species and that particular disclosure of the reference is not enabling. *Impax Laboratories Inc. v. Aventis Pharmaceuticals, Inc.*, 81 USPQ2d 1001 (Fed. Cir. 2006). Applicants respectfully assert that the '358 patent in fact does not enable a method of

using anti-CD40L antibody to treat or prevent pemphigus. The '358 patent discloses "a laundry list of diseases" that anti-CD40L antibody may treat, and offers only speculation that this compound might successfully treat pemphigus.

Applicants further assert that there is no evidence that a person of ordinary skill in the art would find that the '358 patent provides support for a treatment against pemphigus and the gaps in the '358 patent cannot be filled by extrinsic knowledge because no such extrinsic knowledge existed. Specifically, according to the background section of the '358 patent, anti-gp39 (anti-CD40L antibody) was hypothesized to potentially prevent CD40 signaling in B cells, thus inhibiting T-cell dependent antibody responses based on the finding that gp39-CD40 interactions are essential for antibody responses against thymus dependent antigens. (Col. 4, lines 30-44). Theses studies were based on animal models of collagen-induced arthritis and experimental allergic encephalomyelitis (multiple sclerosis) (Col. 4, lines 30-44; Col. 5, lines 21-39), not pemphigus. Neither one of these disease models is related to pemphigus, which represents a group of rare autoimmune mucocutaneous blistering disorders that are mediated by circulating immunoglobulin G (IgG) autoantibodies against the desmosomal cadherins (See page 1 of the instant specification). Applicants respectfully assert that the specification of the '358 patent does not provide an enabled disclosure that an anti-CD40L antibody can be used in the treatment of medical conditions associated with the effects of an autoimmune mucocutaneous blistering disorders. In fact, such disclosure creates "substantial uncertainty" regarding the use of CD40 signaling inhibiting T-cell dependent antibody response compounds in the treatment of pemphigus. The court held that the prior art reference in question is not enabled when a disclosure leaves "substantial uncertainty,". *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1057 (Fed. Cir. 2003).

Therefore, applicants assert that the disclosure of the '358 patent is not enabled for treating or preventing pemphigus by administering anti-CD40L antibody as claimed and thus, as a matter of law, does not anticipate the claimed invention. Reconsideration and withdrawal of the §102(b) rejection to claims 1 and 3 are respectfully requested.

Response to Rejections under 35 U.S.C. §102(e)

Claims 1 and 3 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 7,122,187 to Black, et al. ('187 patent). Specifically, the Examiner contends that the '187 patent discloses antagonistic anti-CD40L antibodies as well as their use in the treatment of autoimmune and non-autoimmune conditions including pemphigus (Office Action – page 7). Accordingly, the Examiner alleges that the claimed invention is anticipated by such disclosure. Applicants respectfully disagree.

Applicants respectfully wish to direct the Examiner's attention to the fact that the '187 patent claims priority to the '358 patent discussed in the previous section. Applicants assert that there is no evidence that a person of ordinary skill in the art would find that the '358 patent provides support for a treatment of pemphigus and the gaps in the '358 patent are not filled by the subsequent filing of the '187 patent. By the same token as discussed above in reference to the '358 patent, applicants assert that the '187 patent does not anticipate a method of using anti-CD40L antibody to treat or prevent pemphigus because the '187 patent just like its parent (the '358 patent) does not enable a person of ordinary skill in the art to treat pemphigus with anti-CD40L antibody.

Therefore, applicants assert that the '189 patent application is not enabled for treating or preventing pemphigus by administering anti-CD40L antibody and thus as a matter of law does not anticipate the claimed invention. Reconsideration and withdrawal of the §102(e) rejection to claims 1 and 3 are respectfully requested.

Claims 1 and 3 have been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Application No. 2004/0038293 to DiPadova, et al. ('293 application). Specifically, according to the Examiner, the '293 application allegedly discloses antagonistic anti-CD40L antibodies as well as their use in the treatment of a plethora of diseases including pemphigus (Office Action – page 7). Accordingly, the Examiner alleges that the claimed invention is anticipated by such disclosure because nothing more is required from the reference "[t]han that it sets forth the substance of invention." (Office Action – page 8). Applicants respectfully disagree.

By the same token as discussed above in reference to the '358 patent, the '293 application similarly discloses "a laundry list of diseases" that CD154 (anti-CD40L antibody) may treat (approximately 140 different disorders listed; See para. [0083]), and offers only speculation that this compound might successfully treat pemphigus. Therefore, applicants assert that the '293 application in fact does not anticipate a method of using anti-CD40L antibody to treat or prevent pemphigus because the '293 application does not enable a person of ordinary skill in the art to treat or prevent pemphigus with anti-CD40L antibody. In fact, the '293 application merely speculates on the subject without any support of extrinsic knowledge. The Examiner is invited to provide evidentiary support to demonstrate that a person of skill in the art would find that the '293 application is enabling for a treatment against pemphigus. Similarly to

the '358 patent, the '293 application does not adequately provide an enabling disclosure that anti-CD40L antibody can be used in the treatment of medical conditions associated with the effects of autoimmune mucocutaneous blistering disorders and creates "substantial uncertainty" regarding use of CD40 signaling inhibiting T-cell dependent antibody response compounds in the treatment of pemphigus. The court held that the prior art reference in question is not enabled when a disclosure leaves "substantial uncertainty,". *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1057 (Fed. Cir. 2003).

Therefore, applicants assert that the '293 patent application is not enabled for treating or preventing pemphigus by administering anti-CD40L antibody and thus as a matter of law does not anticipate the claimed invention. Reconsideration and withdrawal of the §102(e) rejection to claims 1 and 3 are respectfully requested.

Response to Rejections under 35 U.S.C. §103(a)

Claim 3 has been rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 7,122,187 to Black, et al. ('187 patent) or U.S. Patent Application No. 2004/0038293 to DiPadova, et al. ('293 application) in view of *The Merck Manual of Diagnosis and Therapy* (the Merck Manual; Seventeenth Edition) (Office Action – page 9). Applicants respectfully disagree.

Applicants assert that the combination of the '187 patent or the '293 application with the Merck Manual does not teach, disclose, or suggest the method of preventing pemphigus using anti-CD40 antibodies. Specifically, applicants respectfully assert that the Merck Manual does not cure the deficiencies of either the '187 patent or the '293 application noted in the

previous subsections, *i.e.*, lack of enablement for treatment of pemphigus using anti-CD40 antibodies. Thus, applicants contend, that the proposed combination of references fails to teach, disclose, or suggest all of the elements of applicants' claims. For at least these reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claim 3 are respectfully requested.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4025.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4025.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: September 11, 2008 By: _____
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